pressure (MAP, mmHg) was measured during each FBF measurement in the contralateral arm by cuff method. MAP, peak FBF, and maximum vascular conductance (calculated in arbitrary units as FBF/MAP) after arterial occlusion were as follows:

	Before LVAD	1 wk post	8 wks post	Normals
MAP	65 ± 4	93 ± 6*	92 ± 5*	89 ± 9
Peak FBF	5.9 ± 1.6	9.5 ± 4.8	16.4 ± 2.8*	31.5 ± 2.7†
Conductance	0.10 ± 0.03	0.10 ± 0.05	0.18 ± 0.03*	0.36 ± 0.05†

* indicates $p < 0.05$ vs. Before LVAD, † indicates $p < 0.05$ vs. 8 wks post-LVAD

Mean CO increased from 2.3 l/min before LVAD to 5.4 l/min 1 and 8 wks during LVAD support. Despite early normalization of CO and MAP within 1 week after LVAD, the maximum vascular conductance after brachial artery occlusion did not change after 1 week, and remained less than that observed in normal subjects after 8 weeks of LVAD support. The delayed and incomplete reversal of abnormal metabolic vasodilation during long-term continuous LVAD support suggests that mechanisms in addition to reduced CO contribute to decreased metabolic vasodilation in patients with CHF.

901-75 Early Improvement in Congestive Heart Failure Following Correction of Secondary Mitral Regurgitation in End-Stage Cardiomyopathy

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Mitral regurgitation (MR) frequently complicates cardiomyopathy (CM) and contributes to symptoms of congestive heart failure (CHF). This study was undertaken to assess the changes in CHF and left ventricular (LV) systolic performance following mitral valve reconstruction (MVR) in patients with severe MR secondary to end-stage dilated CM. Nine consecutive patients (age 64 ± 10 yrs) with severe LV dysfunction (ejection fraction [EF] 18 ± 5% [10–25%]), severe MR and NYHA Class III (n = 1) or IV (n = 8) CHF despite aggressive medical therapy underwent MVR. All patients were receiving therapy including digoxin, diuretics and afterload reducers. Two patients were awaiting heart transplantation.

There were no operative deaths or deaths on 17 ± 5 (8–24) week follow-up (PostOp). All patients noted symptomatic improvement. NYHA Class improved from 3.9 ± 0.3 pre-operatively (PreOp) to 1.7 ± 0.5 ($p < 0.001$). Diuretic requirements were markedly lower for 5 of 9 patients and stable for the remaining 4. Quantitative 2D echo/Doppler was performed on all patients PreOp and on 8 of 9 patients PostOp. MR was absent or mild on follow-up in all. Matched PreOp and PostOp LV end-diastolic volume (EDV), EF, forward cardiac output (CO) and regurgitant fraction (RF) were compared for change (Δ):

	EDV (cc)	EF (%)	CO (L/min)	RF (%)
PreOp	317 ± 111	18 ± 5	3.1 ± 1.0	70 ± 12
PostOp	291 ± 106	24 ± 9	4.6 ± 0.8	13 ± 10
Δ	−26 ± 31	+6 ± 5	+1.5 ± 0.9	−57 ± 15
p	0.04	0.02	0.004	<0.001

Improvement in CHF occurred after MVR in all patients on short-term follow-up, accompanied by lower LV end-diastolic volume and increased EF and forward cardiac output. Mitral reconstruction may be a new strategy for the treatment of patients with severe MR complicating end-stage cardiomyopathy.

901-76 Antagonism Between Enalapril and Aspirin: Subgroup Analysis of the Cooperative New Scandinavian Enalapril Survival Study II (CONSENSUS II)

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Several drugs have been investigated regarding their effect on mortality when given early after an acute myocardial infarction. The use of angiotensin-converting enzyme (ACE) inhibitors has been studied in several trials with inconsistent results. Aspirin (ASA) has become a well documented therapeutic adjunct in patients with coronary heart disease. Attention has recently been focused on a possible interaction between aspirin and ACE inhibitors. We therefore reanalyzed data from the CONSENSUS II to find any evidence of differential effects of the ACE inhibitor enalapril in subgroups defined by use of ASA at baseline.

Stepwise logistic regression tested the multiplicative interaction. The enalapril-ASA interaction term was a significant predictor of at the end of the study (odds ratio 1.442, $p = 0.047$), and was a borderline-significant predictor of mortality 30 days after randomization (odds ratio 1.450, $p = 0.085$).

We used Rothman synergy index S to examine the postulated interaction with departure from an additive model. S would be equal to unity under additivity, and less than unity when suggesting antagonism. The synergy index was 0.66 (95% confidence interval 0.46 to 0.94) for mortality at the end of the study, and 0.68 (0.44 to 1.04) for 30-day mortality, indicating antagonism between enalapril and ASA. No significant interaction was found regarding nonfatal major events.

Conclusion: We found evidence of enalapril-ASA interaction. Excess mortality occurred when enalapril was randomized to patients using ASA at baseline.

HEMODYNAMICS/SHOCK/ASSIST DEVICES

901-77 Reduction in β_2-Receptor Autoantibody Level in Patients with Idiopathic Dilated Cardiomyopathy During Mechanical Cardiac Assist System Support

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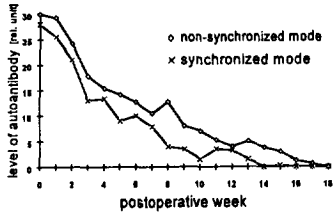
Ten patients (pts) with idiopathic dilated cardiomyopathy were implanted with mechanical left ventricular assist devices (Novacor, TCI) as a bridge to transplantation. The following pre-implantation data was observed: right and left ventricular ejection fraction <20%, x-ray heart-lung ratio >0.68, left ventricular diameter >7.9 cm, and central venous pressure >25 mmHg. All pts were in NYHA class IV and at least on a medium dose of catecholamines. β_2-receptor autoantibody (RAAB) levels were measured by bioassay before implantation and once a week postoperatively. All pts clinically recovered within 6–8 weeks. RAABs were not detected in two pts while in eight pts who preoperatively exhibited a relative level of 25 ± 8 the level decreased during the ensuing 14 weeks to zero in 6 pts. These 6 pts were supported with a device which operated synchronously with the patient's heart rate thus leading to optimal reduction in the afterload of the left ventricle (Fig.). The RAAB level decreased more gradually in the other 2 pts reaching zero three weeks later. A non-synchronized device which did not provide the same degree of afterload reduction was implanted in these pts (Fig.). Although they exhibited a reduction in RAABs and heart rate, a significant improvement in cardiac function, and a decrease in heart size, the two pts with no detectable RAABs exhibited neither an improvement in cardiac function nor a reduction in cardiac diameter.



Conclusion: Mechanical cardiac assist device support not only leads to an improvement in the hemodynamic condition of pts, but apparently also in immunological changes, such as a diminished presentation of specific antigens and a consecutive reduction of autoantibodies, which in the future may be important in assessing the indication for weaning from cardiac assist devices instead of performing transplantation.

901-78 Early Noninvasive Detection of Hypovolemia Secondary to Acute Blood Loss Using Pulse Volume Analysis

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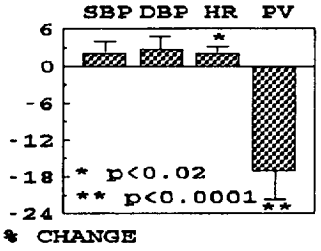
Hypovolemic shock is difficult to recognize in its early stages because clinically significant changes in heart rate (HR), blood pressure (BP), and urine output occur late in its course. This study was conducted to determine if changes in peripheral pulse volume (PV) occur early in acute blood loss, prior to clinically significant changes in HR or BP. PV is defined as the maximum change in volume of a limb segment (e.g. calf) occuring during the cardiac cycle and is measured noninvasively with a digitally enhanced admittance plethysmograph. HR, systolic BP (SBP), diastolic BP (DBP), and calf PV (in microliters, μL) were measured in 35 male blood donors (age = 38.7 ± 11.1 [sd] yrs, weight = 87.7 ± 15.3 [sd] kg) before and after donating a unit of whole blood (the average blood loss was 5.3 ± 0.9 [sd] ml/kg). Pre and post donation measurements were compared using paired Student's t-test. The results (mean ± se) are tabulated below and illustrated above:

	Pre-Donation	Post-Donation	Change	Significance
HR (/min)	68.5 ± 1.5	69.8 ± 1.5	1.4 ± 0.6	$p < 0.02$
SBP (mmHg)	143.1 ± 2.5	145.8 ± 3.1	2.9 ± 2.3	n.s.
DBP (mmHg)	73.2 ± 2.0	75.7 ± 1.7	1.9 ± 1.5	n.s.
PV (μL)	1151 ± 64	954 ± 39	−197 ± 53	$p < 0.0001$



There were no significant changes in either SBP or DBP. The HR increased significantly, but by only 2.0% ($p < 0.02$). The PV decreased by 17.1% ($p < 0.0001$), which is 8.6 times greater than the percent change in heart rate ($p < 0.01$). The PV decrease correlated with the blood loss per kg ($r = 0.46$, $p < 0.01$). We conclude that a significant change in PV occurs with relatively minor blood loss. Pulse volume analysis may therefore provide an early indication of hypovolemia due to acute blood loss.

HYPERTENSION

901-79 Borderline Isolated Systolic Hypertension and Subsequent Risk of Cardiovascular Disease

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Guidelines are unclear about treatment of borderline isolated systolic hypertension, defined as both systolic BP 140–159 mmHg and diastolic BP < 90 mmHg. We investigated the association between borderline isolated systolic hypertension and subsequent risk of myocardial infarction (MI), stroke, cardiovascular death, and the combined endpoint of important cardiovascular events (nonfatal MI, nonfatal stroke or cardiovascular death) among 22,071 men age 40–84 years followed prospectively for an average of 10.7 years in the Physician's Health Study. Baseline BP and cardiovascular risk factors were available from completed questionnaires on 16,678 men among whom 960 subsequently had an incident important cardiovascular event. In proportional hazards models adjusting for other cardiovascular risk factors, the relative risks were calculated for those with borderline isolated systolic hypertension relative to those with both systolic BP < 140 mmHg and diastolic BP < 90 mmHg. These relative risks were 1.05 (95% confidence interval CI 0.80 to 1.36) for MI, 1.68 (95% CI 1.24 to 2.26) for stroke, 1.61 (95% CI 1.19 to 2.18) for cardiovascular death, and 1.32 (95% CI 1.11 to 1.58) for the combined endpoint of important cardiovascular events. These associations were not altered by an analysis excluding participants who reported baseline treatment for hypertension.

Conclusion: Borderline isolated systolic hypertension is associated with a significantly increased risk of subsequent important cardiovascular events.

901-80 Auscultatory Gaps and Target Organ Damage in Hypertensive Patients

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Auscultatory gaps are a common finding in clinical practice but their clinical and prognostic importance has never been assessed. To examine the relation of auscultatory gaps to left ventricular and arterial structure and function, wideband external pulse recordings during cuff deflation to detect auscultatory gaps and ultrasonographic examination of left ventricle and extracranial carotid artery were performed in 168 unmedicated, asymptomatic hypertensive subjects. Vascular stiffness was also evaluated by simultaneous carotid pressure waveforms obtained by applanation tonometry of the contralateral carotid artery. Auscultatory gaps were present in 21% of the population and were associated with older age (64 ± 11 vs 55 ± 13 years, $p < 0.0005$), female gender (66 vs 44%, $p < 0.05$) and increased arterial stiffness (beta = 8.5 ± 4.6 vs 5.8 ± 3.2, $p < 0.005$). Differences in arterial stiffness persisted after controlling for the confounding effects of age and gender. The prevalence of atherosclerotic plaques was more than two-fold increased among subjects with gaps (50 vs 22%, $p < 0.005$). No significant differences were found in left ventricular structure and function between the subjects with and without gaps. The two populations had similar systolic and diastolic blood pressures, serum lipid levels and smoking history. Logistic regression analysis including age in the model indicated that only female gender, beta (an index of arterial stiffness) and the presence of plaque were independently related to the presence of auscultatory gaps. This study provides the first evidence that auscultatory gaps are related to the presence of carotid atherosclerosis and to increased arterial stiffness in hypertensive patients, independently of age. Although these observations need to be confirmed by prospective studies they suggest a prognostic relevance of the auscultatory gaps.

901-81 Association of a Molecular Variant of the Angiotensinogen Gene and Hypertension

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A molecular variant of the angiotensinogen gene encoding methionine instead of threonine at position 174 (T174M) has been associated with essential hypertension (HTN) in case-control studies. We examined the relations of the T174M allele with HTN in 1401 subjects (707 men, 694 women) from the Framingham Offspring Study (mean age 50.5, range 25–78 years). Pooled- and sex-specific simple association analyses revealed no relation between hypertension status and presence or absence of T174M. Conditional logistic regression was used to analyze the relations of T174M to HTN in 143 sibships in which at least 1 sibling had HTN. After adjusting for sex and age, presence of T174M was associated with a nonsignificant increase in probability of HTN (OR 1.89, 95% CI 0.83–4.29, $p = 0.13$). Analysis of 25 affected sibling-pairs with severe HTN suggested an excess sharing of the T174M allele ($p = 0.056$).

Clinical status	Genotype		
	AA (n = 1118)	Aa (n = 253)	aa (n = 30)
Mild HTN (%)	24.0	24.9	20.0
Severe HTN (%)	12.0	13.8	16.7

AA = normal, Aa = presence of 1 T174M allele, aa = presence of 2 T174M alleles. Severe HTN = systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg or use of ≥2 anti-HTN medications. Mild HTN = systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg or use of a single anti-HTN medication.

Conclusions: In this large noninstitutionalized sample, we did not find an association between the T174M allele and HTN. In a subset of 25 sibships with severe HTN, however, genetic linkage between the angiotensinogen locus and severe HTN was suggested.

ISCHEMIC HEART DISEASE — CHRONIC/SILENT ISCHEMIA

901-82 A Multicenter Controlled Trial of a Novel Metabolic Active Compound (Ranolazine) in Chronic Stable Angina Patients

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Ranolazine is a new antianginal agent believed to reduce oxygen demand through its metabolic action without effects on blood pressure, heart rate or cardiac function. It was evaluated in a randomized, double-blind, placebo-controlled, crossover trial with an extended-period Latin square design (5 one week periods). During a placebo phase, 312 patients with chronic stable angina (≥3 months) receiving multiple antianginals were withdrawn from ≥1 antianginal drugs. After their exercise time had shortened by ≥1.0 mins they were randomized to receive either ranolazine 267 mg tid, 400 mg bid, 400 mg tid or placebo during each study period. After 1 week of treatment exercise tolerance (Bruce protocol) and plasma ranolazine levels were measured at peak (1 hr after dosing) and at trough (8 [tid] or 12 [bid] hr after dosing).

Results at Peak Ranolazine Blood Level

Parameter (in sec.)	Ranolazine Dose Group minus Placebo Group Responses		
	267 mg tid	400 mg bid	400 mg tid
Time to angina	23 (8, 38)**	19 (4, 34)*	19 (4, 34)*
Exercise duration	12 (2, 23)	10 (−0.6, 20)	10 (−0.1, 20)
Time to 1 mm ST	25 (11, 39)**	17 (3, 31)*	22 (8, 36)**
% with adverse event	1.1%	−0.3%	1.9%

Mean (95% CI) * $P < 0.05$, ** $P < 0.01$, STD = ST Segment Depression

Ranolazine significantly increased times to onset of both angina and ST segment depression at all doses tested. All exercise parameters were significantly ($P \leq 0.01$) improved with ranolazine at peak plasma levels compared with placebo as ranolazine plasma levels ranged from 1,350 to 2,130